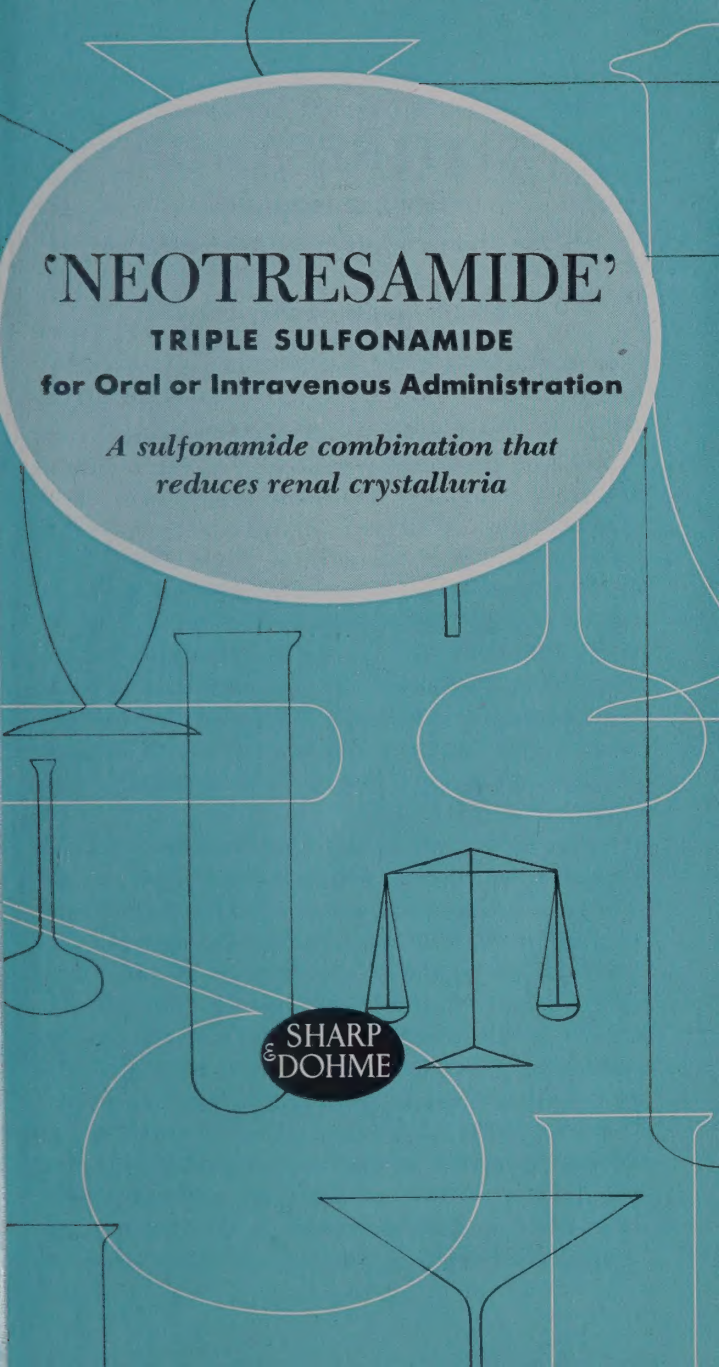
'NEOTRESAMIDE'

TRIPLE SULFONAMIDE

for Oral or Intravenous Administration

A sulfonamide combination that reduces renal crystalluria



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The prevention of toxic reactions due to sulfonamide therapy, or reduction of the incidence of such reactions, has been the subject of extensive studies. Renal complications constitute the most important of these toxic effects, since they appear to occur more frequently and have more serious consequence.

Crystalluria is the primary factor causing renal complications in patients treated with sulfonamides. Although a chemical nephrotoxic action also has been implicated, it is considered of less importance[1,2] and little is known of its mechanism of action.[3]

The formation of sulfonamide concretions in the urinary tract depends for the most part on the solubility and concentration of the compound in the tubular urine. Crystalluria thus may be prevented or diminished by increasing the solubility of the sulfonamide (by alkalization) or by decreasing its concentration in the urine (by forcing fluids).

Alkalization and forcing of fluids, however, have certain disadvantages.[1,3,4,5] It is not always possible to maintain an alkaline urine even with the use of large amounts of alkalizing salts, and it frequently is difficult to force fluids in seriously ill patients. Effective amounts

of fluid or alkalizing salts tend to lower the plasma concentration of the sulfonamide by rapid elimination of the latter in the urine or by reason of the fact that the salt competes successfully with the sulfonamide for reabsorption in the renal tubule. Furthermore, when sodium bicarbonate is administered, retention of the sodium with or without alkalosis may occur. Also, sodium salts and excessive fluid intake are inadvisable in patients with cardiac decompensation or renal impairment.

Development of 'Neotresamide' Triple Sulfonamide

These disadvantages may be overcome by the simultaneous administration of two or more sulfonamides for effective treatment with concomitant elimination or diminution of renal complications. The Medical Research Division of Sharp & Dohme therefore presents 'Neotresamide' Triple Sulfonamide.

'NEOTRESAMIDE' TABLETS
(For Oral Administration)
Each 0.5 Gm. tablet contains:

Sulfamerazine	**0.1 Gm.**
Sulfadiazine	**0.2 Gm.**
Sulfamethazine	**0.2 Gm.**

'NEOTRESAMIDE' STERILE SOLUTION, 6%
(For Intravenous Administration)
Each 50 cc. contains:

Sodium Sulfamerazine	**0.6 Gm.**
Sodium Sulfadiazine	**1.2 Gm.**
Sodium Sulfamethazine	**1.2 Gm.**
Distilled Water	**q.s 50 cc.**

The therapeutic principle of administering two sulfonamides and thereby reducing the risk of

concrement formation has been employed for several years by Hagerman,[6,7] Herlitz,[8] and Werkö[9] in treating gonorrhea. The absence of toxic reactions, including crystalluria, also was reported by Minetto,[10] who administered a combination of two sulfonamides for the treatment of pneumonia.

The rationale for this combined therapy is based on the observation that two or more sulfonamides dissolve independently of one another; that is, one sulfonamide has little effect on the other with respect to solubility in the same solution.[1,2,11-13] Therefore, with a mixture of two or more sulfonamides the maximum concentration in solution is equal to the sum of the solubilities of the individual drugs. This is true even with closely related chemical compounds such as sulfadiazine and its monomethyl and dimethyl derivatives, sulfamerazine and sulfamethazine, and it applies to the free as well as the acetylated homolog of the sulfonamides.[3,12,14] This observation with respect to the acetylated derivative is particularly significant, since the latter form is the more likely to cause crystalluria.[3]

Advantages of 'Neotresamide' Triple Sulfonamide

The advantages to be obtained from the use of a sulfonamide mixture in place of a single compound were confirmed by evaluation of *in vitro* antibacterial efficacy and acute and chronic toxicity in animals. The antibacterial action of a sulfonamide mixture corresponds to the total concentration of the drugs present, and in some instances potentiation has been noted.[11,12,14] A remarkable decrease in both acute and chronic

toxicity was observed in animals that received two sulfonamides simultaneously in one-half the dosage of each compound when given singly, and an even greater decrease in toxicity was obtained with a triple sulfonamide mixture. The lower toxicity was ascribed to diminution in renal obstruction as shown by analysis of nonprotein nitrogen blood levels and postmortem findings.

Studies in laboratory animals and human subjects also showed that absorption and excretion of sulfonamides administered simultaneously proceeds on an independent basis.[1,2,12,14] In fact, absorption is more complete, resulting in high blood levels, and excretion is more complete and more rapid. Thus, therapeutically effective blood levels may be attained and maintained, with rapid elimination after discontinuance of therapy. Rapid excretion in the presence of high blood levels gives added protection against intrarenal obstruction.

Clinical Evaluation

The therapeutic application of combinations of two or three sulfonamides has been investigated by a number of clinicians.[1,2,5-10,13-18] Lehr[1,2] administered a combination of two sulfonamides to 70 adults and more than 200 children and infants with acute bacterial infections. Alkalizing salts and forcing of fluids were not employed as adjunctive measures. Clinical improvement appeared to be more rapid in comparison with results obtained hitherto with administration of either drug separately, and it was possible to shorten the treatment period in some instances. This indicated a possible *in vivo* potentiation of antibacterial activity.

Only a few instances of crystalluria were noted and these were associated with a high sulfonamide concentration in acid urine. There was no evidence of massive crystalluria, whereas the separate administration of sulfadiazine or sulfathiazole has resulted in persistent and massive renal concretions. No sign of renal irritation such as hematuria, casts, or oliguria was observed.

Since allergic reactions do not depend on the size of the dose, it might be expected that the incidence of such reactions would increase with the joint administration of two or more sulfonamides. Actually, a lower incidence of sensitization has been encountered. This probably is due to the fact that administration of the combined sulfonamides can be discontinued as a rule before the time when allergic reactions appear most frequently.[1,2]

A triple sulfonamide combination has been employed in treating several hundreds of patients with acute pneumonia with excellent therapeutic results and no evidence of renal concretions.[14] Similar good results have been obtained in gonorrhea.[14,15]

On the basis of the above mentioned studies,[12, 14] it would appear that the possibility of crystalluria is eliminated almost entirely with the use of a triple sulfonamide combination, thus obviating in most instances the necessity of employing such adjuvant measures as alkalization. This remarkable reduction in the incidence of crystalluria is advantageous when it is desirable to administer a larger than ordinary dosage for treatment of resistant infections, since the danger of crystalluria is not thereby increased.[14]

Sulfamethazine rather than sulfathiazole has been included in 'Neotresamide' Triple Sulfonamide because of the relatively high incidence of toxic reactions following sulfathiazole therapy (18 per cent), and in accordance with the deletion of this compound from New and Nonofficial Remedies.[19]

Numerous reports have appeared in the medical literature with respect to the clinical efficacy and lack of toxicity of sulfamethazine (4,6-dimethyl-2-sulfanilamidopyrimidine). With respect to acute and chronic toxicity, this compound appears to be similar to sulfamerazine and sulfadiazine.[20] On the basis of solubility and renal toxicity, however, sulfamethazine and sulfamerazine may be more desirable drugs than sulfadiazine. "Sulfamethazine seems to be devoid of renal toxicity, irrespective of the concentration of this drug in the blood. Sulfamerazine has decidedly less renal toxicity than sulfadiazine," the most important factor apparently being the greater solubility of sulfamethazine and sulfamerazine in acid urine.[20] In formulating a triple sulfonamide preparation such as 'Neotresamide' Tablets and 'Neotresamide' Sterile Solution, therefore, the addition of sulfamethazine should be of definite value in preventing renal toxicity and enhancing the therapeutic efficacy of the combination.

Clinical Indications

'Neotresamide' Tablets and 'Neotresamide' Sterile Solution are recommended for the treatment of infections in which sulfamerazine,[21-25] sulfadiazine,[26-30] or sulfamethazine[31-35] alone is indicated.

Dosage and Administration

'NEOTRESAMIDE' TABLETS

Adults: Initial dose 3.0 Gm. (6 tablets) followed by 1.0 Gm. (2 tablets) every 4 hours. The 2 a.m. dose may be omitted in the majority of instances when a sufficient sulfonamide level has been established. When definite clinical improvement has been obtained, as indicated by defervescence, this maintenance dosage may be decreased to 1.0 Gm. every 6 hours.

Children: *Up to 6 months*—Initial dose 0.75 Gm. (1½ tablets) followed by 0.25 Gm. (½ tablet) every 6 hours.

½ to 3 years—Initial dose 1.5 Gm. (3 tablets) followed by 0.5 Gm. (1 tablet) every 6 hours.

3 to 10 years—Initial dose 3.0 Gm. (6 tablets) followed by 1.0 Gm. (2 tablets) every 6 hours.

The maintenance dose of 'Neotresamide' Tablets should be continued until definite clinical improvement has been obtained, as indicated by defervescence.

The recommended dosage may be adjusted depending upon the nature of the illness and the condition of the patient, in accordance with clinical judgment.

'NEOTRESAMIDE' STERILE SOLUTION

The intravenous administration of 'Neotresamide' Triple Sulfonamide is indicated in the treatment of:

(a) critically ill patients who require immediate and adequate medication.

(b) patients in whom it is impossible to obtain a satisfactory therapeutic level of free sulfonamide by means of oral administration.

When possible, administration of 'Neotresamide' Tablets should be commenced simultaneously with the intravenous administration of 'Neotresamide' Sterile Solution, or immediately thereafter, and parenteral administration should be discontinued as soon as a satisfactory blood level can be maintained by oral administration. 'Neotresamide' Sterile Solution should be injected slowly under aseptic conditions either by means of a large syringe or as in an intravenous infusion. Since the solution is strongly alkaline, extravasation during intravenous administration should be avoided.

Administer approximately 0.05 Gm. of triple sulfonamide per kilogram of body weight as the initial dose. In order to maintain an effective level of free drug, oral therapy (1.0 Gm., or two 'Neotresamide' Tablets, every 4 hours) should be started immediately after completion of the intravenous injection. The following table may be referred to for convenience in determining the dose of 'Neotresamide' Sterile Solution:

Weight in Kilograms	Weight in Pounds	Dose in Grams	Dose in cc. of 6% Solution
5 Kg.	11 lb.	0.25 Gm.	4.0 cc.
10 Kg.	22 lb.	0.5 Gm.	8.0 cc.
20 Kg.	44 lb.	1.0 Gm.	16.5 cc.
30 Kg.	66 lb.	1.5 Gm.	25.0 cc.
40 Kg.	88 lb.	2.0 Gm.	33.0 cc.
50 Kg.	110 lb.	2.5 Gm.	41.5 cc.
60 Kg.	132 lb.	3.0 Gm.	50.0 cc.
70 Kg.	154 lb.	3.5 Gm.	58.0 cc.
80 Kg.	176 lb.	4.0 Gm.	66.5 cc.
90 Kg.	198 lb.	4.5 Gm.	75.0 cc.

If, in rare instances, it is impossible to maintain an effective level by oral administration alone, a second intravenous dose of about 0.05 Gm. of triple sulfonamide per kilogram of body weight should be given from 6 to 12 hours after the initial injection. Before repeating an intravenous dose, the concentration of sulfonamide in the blood should be determined. The number of doses necessary will depend, of course, on the size of each dose and the maintained blood levels.

Warnings Concerning Parenteral Administration

1. Do not administer 'Neotresamide' Sterile Solution in connection with a blood transfusion; the intravenous injection of the triple sulfonamide should be a separate and distinct procedure. In general, the addition of 'Neotresamide' Sterile Solution to transfusions of citrated blood should be avoided because of the possibility of causing undesirable alterations in the blood owing to the high alkalinity of the solution.

2. If possible, avoid repeated injections.

3. 'Neotresamide' Sterile Solution should not be administered intraspinally or by rectum.

4. Constant supervision of the patient by the physician is essential.

Although it is anticipated that the joint use of the three sulfonamides in 'Neotresamide' Tablets and 'Neotresamide' Sterile Solution will reduce the occurrence of crystalluria to a minimum, the added protection of alkalizing salts and fluids is nevertheless recommended when practical, especially in older patients and

in those receiving high doses for prolonged periods. The precautions usually employed in sulfonamide therapy should be observed. The total sulfonamide concentration in blood and urine may be determined by standard procedures, as described in an informative brochure that is available on request.

How Supplied

'Neotresamide' Tablets Triple Sulfonamide, 0.5 Gm. each, are supplied in bottles of 100 and 1,000.

Sterile Solution 'Neotresamide' Triple Sulfonamide, 6%, 3.0 Gm. in 50 cc., is supplied in packages of one ampul and in lots of 6, 25 and 100 ampuls.

References

1. Lehr, D., J. Urol. *55*:548, May 1946.
2. Lehr, D., Slobody, L., and Greenberg, W., J. Pediat. *29*:275, Sept. 1946.
3. Flippin, H. F., and Reinhold, J. G., Ann. Int. Med. *25*:433, Sept. 1946.
4. Editorial, New England J. Med. *236*:842, May 29, 1947.
5. Snyder, L. J., Proc. Central Soc. Clin. Research *20*:70 (1947).
6. Hagerman, G., Nordiskt med. Ark. *22*:1093, 1223 (1944).
7. Hagerman, G., Nordiskt med. Ark. *24*:1944 (1944).
8. Herlitz, S., Nordiskt med. Ark. *22*:1226 (1944).
9. Werkö, L., Svenska Läkartidn. *42*:746 (1945).
10. Minetto, L. P., New York State J. Med. *44*:2022, Sept. 15, 1944.
11. Lehr, D., Proc. Soc. Exper. Biol. & Med. *58*:11, Jan. 1945.
12. Lehr, D., Proc. Soc. Exper. Biol. & Med. *64*:393, April 1947.
13. Lehr, D., Brit. M. J. *2*:943, Dec. 13, 1947.
14. Frisk, A. R., Hagerman, G., Helander, S., and Sjögren, B. Brit. M. J. *1*:7, Jan. 4, 1947.
15. Nilzen, A., Svenska Läkartidn. *43*:1816 (1946).
16. Lehr, D., Brit. M. J. *2*:543, Sept. 18, 1948.
17. Slobody, L. B., Lehr, D., and Willner, M. M., Pediatrics *2*:58, July 1948.
18. Shore, P. D., Flippin, H. F., and Reinhold, J. G., Am. J. M. Sc. *218*:80, July 1949.
19. Report of Council on Pharmacy and Chemistry, J.A.M.A. *141*:264, Sept. 24, 1949.
20. Schmidt, L. H., Hughes, H. B., and Badger, E. A., J. Pharmacol. & Exper. Therap. *81*:17, May 1944.
21. Flippin, H. F., Gefter, W. I., Domm, A. H., and Clark, J. H., Am. J. M. Sc. *206*:216, Aug. 1943.
22. Anderson, D. G., Oliver, C. S., and Keefer, C. S., New England J. Med. *230*:369, March 30, 1944.
23. Genecin, A., Austrian, R. C., and Nelson, R. A., Bull. Johns Hopkins Hosp. *76*:112, March 1945.
24. Reinhold, J. G., Flippin, H. F., Zimmerman, J. J., Gefter, W. I., and Riddler, J. G., J. Clin. Investigation *24*:352, May 1945.
25. Forbes, G. B., Perley, A., and Dehlinger, J., J. Pediat. *28*:24, Jan. 1946.
26. Finland, M., Strauss, E., and Peterson, O. L., J.A.M.A. *116*:2641, June 14, 1941.
27. Finland, M., Peterson, O. L., and Goodwin, R. A., Jr., Ann. Int. Med. *17*:920, Dec. 1942.
28. Shackman, N. H., and Bullowa, J. G. M., Arch. Int. Med. *72*:329, Sept. 1943.
29. Marangoni, B. A., and D'Agati, V. C., Am. J. M. Sc. *207*:67, Jan. 1944.
30. Appelbaum, E., Am. J. M. Sc. *207*:492, April 1944.
31. Loughlin, E. H., Bennett, R. H., and Flanagan, M. E., J. Lab. & Clin. Med. *29*:568, June 1944.
32. Volini, I. F., Engbring, G. M., and Schorsch, H. A., Arch. Int. Med. *75*:168, March 1945.
33. Morgan, T. N., and Wylie-Smith, R., Lancet *2*:731, Dec. 11, 1943.
34. Melton, G., Lancet *1*:277, Feb. 26, 1944.
35. Ramsay, W. A., Luxton, R. W., Steiner, P., and Smith, G. S., Lancet *1*:78, Jan. 20, 1945.

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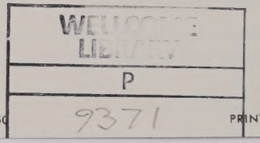
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19. Report of Council on Pharmacy and Chemistry, J.A.M.A. *141*:264, Sept. 24, 1949.
20. Schmidt, L. H., Hughes, H. B., and Badger, E. A., J. Pharmacol. & Exper. Therap. *81*:17, May 1944.
21. Flippin, H. F., Gefter, W. I., Domm, A. H., and Clark, J. H., Am. J. M. Sc. *206*:216, Aug. 1943.
22. Anderson, D. G., Oliver, C. S., and Keefer, C. S., New England J. Med. *230*:369, March 30, 1944.
23. Genecin, A., Austrian, R. C., and Nelson, R. A., Bull. Johns Hopkins Hosp. *76*:112, March 1945.
24. Reinhold, J. G., Flippin, H. F., Zimmerman, J. J., Gefter, W. I., and Riddler, J. G., J. Clin. Investigation *24*:352, May 1945.
25. Forbes, G. B., Perley, A., and Dehlinger, J., J. Pediat. *28*:24, Jan. 1946.
26. Finland, M., Strauss, E., and Peterson, O. L., J.A.M.A. *116*:2641, June 14, 1941.
27. Finland, M., Peterson, O. L., and Goodwin, R. A., Jr., Ann. Int. Med. *17*:920, Dec. 1942.
28. Shackman, N. H., and Bullowa, J. G. M., Arch. Int. Med. *72*:329, Sept. 1943.
29. Marangoni, B. A., and D'Agati, V. C., Am. J. M. Sc. *207*:67, Jan. 1944.
30. Appelbaum, E., Am. J. M. Sc. *207*:492, April 1944.
31. Loughlin, E. H., Bennett, R. H., and Flanagan, M. E., J. Lab. & Clin. Med. *29*:568, June 1944.
32. Volini, I. F., Engbring, G. M., and Schorsch, H. A., Arch. Int. Med. *75*:168, March 1945.
33. Morgan, T. N., and Wylie-Smith, R., Lancet *2*:731, Dec. 11, 1943.
34. Melton, G., Lancet *1*:277, Feb. 26, 1944.
35. Ramsay, W. A., Luxton, R. W., Steiner, P., and Smith, G. S., Lancet *1*:78, Jan. 20, 1945.

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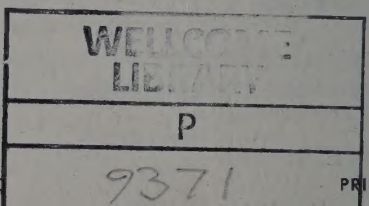

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